Remarks

With the entering of the above amendments, claims 2, 3, 8, 12 and 13-38, of which claims 2, 8, 12 and 35 are in independent form, are pending. Applicants amended claims 2, 3, 8 and 12; canceled claim 4; and added claims 13-35. No new matter was added. For example, claim 21 recites a bone graft composition further comprising a bone allograft, e.g., cancellous bone. Support can be found, e.g., at page 6, line 1-10, of the specification.

Claim Rejections - 35 U.S.C. § 112

The Examiner rejected claims 2 and 8 under 35 U.S.C. § 112, second paragraph, as being indefinite. In light of the amendments to claims 2 and 8, Applicants request that the rejection under § 112, second paragraph, be reconsidered and withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claim 2

The Examiner rejected claim 2 under 35 U.S.C. § 102(b) as anticipated by WO 96/39203 ("Jefferies"). Amended claim 2 recites a bone graft substitute composition including calcium sulfate, a mixing solution (e.g., water), a cellulose derivative and demineralized bone matrix.

Jefferies describes multiple alternative bone graft compositions. For example, Jefferies describes one composition including demineralized bone that has been treated with a calcium salt (see page 16). Jefferies describes a long list of calcium salts; calcium sulfate is on the list (see page 17). However, Jefferies does not disclose that this composition also includes a cellulose derivative or a component akin to a cellulose derivative.

Subsequently, Jefferies describes an alternative osteogenic composition including between 60 percent and 95 percent demineralized bone (see page 20). Jefferies lists examples of materials that can be included with the demineralized bone in the composition (id.). Methylcellulose and hydroxymethyl cellulose are included in the list, as "other biocompatible excipients". But calcium sulfate is not included in the list.

Applicants also note that Jefferies describes 43 examples, none of which include either calcium sulfate or a cellulose derivative, let alone the two in combination.

A reference can anticipate a composition claim only if the reference discloses a composition including all the components required by the claim. Jefferies does not disclose a

composition including both calcium sulfate and a cellulose derivative. As a result, applicants request that the 35 U.S.C. § 102(b) rejection of claim 2 be withdrawn.

Claim 8

The Examiner rejected claim 8 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,385,887 ("Yim"). Amended claim 8 recites a bone graft substitute composition including calcium sulfate, a mixing solution, a cellulose derivative, and a bioactive agent selected from growth factors, bone autograft, analgesics, bone marrow, bone allograft, and parenchymal and mesenchymal cells.

Yim does not disclose a composition containing one of the bioactive agents listed in claim 8. Accordingly, Applicants request that the 35 U.S.C. § 102(b) rejection of claim 8 be withdrawn.

Claim Rejections - 35 U.S.C. § 103

The Examiner rejected claims 2-4 and 12 under 35 U.S.C. § 103(a) as being unpatentable over Yim, O'Leary et al., U.S. Patent No. 5,484,601 ("O'Leary") and Jefferies taken as a whole. As a practical matter, the Examiner picks and chooses components at random from compositions described in the three references and then combines them to reconstruct the compositions covered by the claims, reasoning that "all of the claimed components are well known to be included in bone graft composition, within the amounts claimed" (see office action, ¶ 8). This is an inappropriate basis for a rejection based on 35 U.S.C. § 103(a) because the Examiner has not provided any explanation of how these references suggest that the components be selected and combined to achieve the compositions required by the claims. It is black letter law that the Examiner must explain why the prior art suggests the specific combination of components required by the claims. As the court explained in In re Wainer, 154 U.S.P.Q. 173, 178 (C.C.P.A. 1967) (emphasis in original):

> The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis.

The fact that the teachings in references could be combined to obtain the claimed compositions is not a sufficient basis for obviousness. See Gentry Gallery, Inc. v. Berkline Corp., 45 U.S.P.Q.2d 1498, 1502 (Fed. Cir. 1998), where the court reasoned:

> [T]he mere possibility that the Talley and Kanowsky references could have been combined is insufficient to demonstrate that the claimed invention would have been obvious.

Despite the failure of the Examiner to provide an appropriate basis for combining the components described in the cited references, in the interests of advancing prosecution, applicants will explain why the references, alone or in combination, do not suggest the compositions covered in particular by independent claims 2, 8, and 12.

Jefferies was discussed above. Jefferies only mentions a cellulose derivative once, as a potential optional excipient (carrier) for a composition including between 60% and 90% demineralized bone by weight. Jefferies does not list calcium sulfate, or any calcium salt, as a potential optional component for this composition. Jefferies earlier discussed a different type of composition including demineralized bone that has been treated with calcium sulfate, but this is a different type of composition that does not include an excipient like a cellulose derivative. Thus, Jefferies does not suggest the compositions covered by claims 2, 8, and 12.

Applicants also note that the compositions covered by claim 12 includes less than 50% demineralized bone; the cellulose derivative-containing composition described by Jefferies includes more than 60% demineralized bone in combination. Likewise, the compositions described by Jefferies including demineralized bone treated with calcium includes very low levels of calcium, far below the "80-120 parts" (relative to the amounts of other components) required by claim 12.

Yim discloses formulations including "autogenous blood" as a protein sequestering agent, a "porous particulate polymer", an osteogenic protein, and calcium sulfate that address as specific problems in prior art formulations that did not include calcium sulfate. Specifically, Yim says (col. 2, lines 51-65):

> In U.S. Pat. No. 5,171,579, it is disclosed that osteogenic proteins can be sequestered at a site where bone inducing activity is desired using autogenous blood, without using antifibrinolytic agents, provided that a porous particulate polymer matrix is incorporated into the formulation. To reduce the preparation

> time and improve the above formulation's handling characteristics, Applicants have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate (CaSO.sub.4 *1/2H.sub.2 O), also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS reduces setup time and provides improved moldability and consistency of the resulting formulation.

Yim's formulations are designed for sequestering the osteogenic protein for a sufficient time to allow the protein to induce new bone growth. Yim also mentions that the formulation optionally may include a cellulosic material as an additional "protein sequestering agent."

Yim does not suggest including either the demineralized bone matrix required by claims 2 and 12 or the bioactive agent (from the list) required by claim 8 in his composition. Yim's formulations are specific and already include the porous particulate polymer and osteogenic protein. There is no reason to include demineralized bone matrix in the formulation; in fact, adding demineralized bone matrix would significantly change the formulation.

Moreover, a person of ordinary skill in the art would not be motivated to combine the teachings of Yim with those of Jefferies to obtain the claimed composition. For example, Yim uses calcium sulfate to improve moldability and consistency, whereas Jefferies uses calcium salts (in one composition) for a totally different reason, to treat demineralized bone. Likewise, Yim uses an optional cellulose derivative as an additional "protein sequestering agent", whereas Jefferies uses a cellulose derivative (in one composition) as a excipient. It is pure hindsight to combine the teachings of these references.

O'Leary describes a "flowable demineralized bone powder" composition for use in bone repair. The composition optionally can include a "thickener" such as a cellulose derivative. O'Leary does not teach or suggest including calcium sulfate in the composition, as required by claims 2, 8, and 12.

A person of ordinary skill in the art would not have been motivated to combine the teachings of O'Leary with those of either Yim or Jefferies. For example, O'Leary uses a cellulose derivative as a thickener, whereas Yim uses a cellulose derivative as an optional "protein sequestering agent" and Jefferies uses a cellulose derivative (in one composition) as an excipient. Moreover, O'Leary does not disclose that he is seeking to add calcium to

demineralized bone as Jefferies does in one composition, or that he is addressing a moldability or consistency problem like the problem addressed by Yim. Once again, it is pure hindsight to combine the teachings of these references.

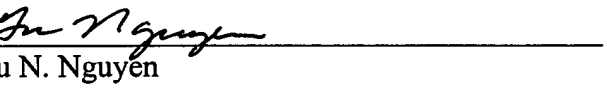
Conclusion

Applicants submit that the claims are in condition for allowance, which action is requested.

Enclosed are a Revocation and New Power of Attorney, and a Supplemental Information Disclosure Statement. Applicants request that the Examiner consider all the cited references. Also enclosed is a marked-up version of the amendments being made by the current response. Also enclosed is a check for excess claim fees. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: May 9, 2001



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Version with markings to show changes made

In the claims:

Claim 4 has been cancelled.

Claims 2, 3, 8, and 12 have been amended.

2. (Twice Amended) A bone graft substitute composition comprising:

(a) calcium sulfate;

(b) a mixing solution [selected from the group consisting of sterile water, inorganic salts, and cationic surface active agents including sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate];

(c) a [plasticizing substance selected from the group consisting of] cellulose derivative [derivatives including sodium carboxymethylcellulose, methycellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxethylcellulose and cellulose acetate butyrate, and higher molecular weight alcohols including glycerol and vinyl alcohols]; and

(d) demineralized bone matrix.

3. (Amended) The bone graft substitute composition of claim 2_2 [in which said composition is] comprising approximately 40% demineralized bone matrix by dry weight.

8. (Amended) A bone graft substitute composition comprising:

(a) calcium sulfate;

(b) a mixing solution [selected from the group consisting of sterile water, inorganic salts, and cationic surface active agents including sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate];

(c) a [plasticizing substance selected from the group consisting of] cellulose derivative [derivatives including sodium carboxymethylcellulose, methycellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxethylcellulose and cellulose acetate butyrate, and higher molecular weight alcohols including glycerol and vinyl alcohols]; and

(d) a bioactive agent selected from the group consisting of [demineralized bone matrix,] growth factors, [hyaluronic acid, bone morphogenic proteins,] bone autograft, [therapeutic agents,] analgesics, [and] bone marrow, bone allograft, and parenchymal and mesenchymal cells.

12. (Twice Amended) A bone graft substitute composition comprising:

(a) approximately 80-120 parts medical grade calcium sulfate hemihydrate by weight;

(b) approximately 21-250 parts sterile water by weight;

(c) approximately 1-40 parts [sodium] carboxymethylcellulose by weight; and

(d) approximately 10-100 parts demineralized bone matrix by weight.

Claims 13-38 have been added:

13. (New) The bone graft substitute composition of claim 2, wherein the mixing solution is selected from a group consisting of sterile water, an inorganic salt, and a cationic surface active agent.

14. (New) The bone graft substitute composition of claim 13, wherein the cationic surface agent is selected from a group consisting of sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate.

15. (New) The bone graft substitute composition of claim 2, wherein the mixing solution comprises sterile water.

16. (New) The bone graft substitute composition of claim 2, wherein the cellulose derivative is selected from a group consisting of sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose and cellulose acetate butyrate.

17. (New) The bone graft substitute composition of claim 2, wherein the cellulose derivative comprises carboxymethylcellulose.

18. (New) The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate.

19. (New) The bone graft substitute composition of claim 2, wherein the calcium sulfate comprises calcium sulfate hemihydrate, the mixing solution comprises sterile water, and the plasticizing substance comprises carboxymethylcellulose.

20. (New) The bone graft substitute composition of claim 19, comprising approximately 100 parts calcium sulfate hemihydrate by weight, approximately 11.1 parts carboxymethylcellulose by weight, approximately 162 parts water by weight, and approximately 69.4 parts demineralized bone matrix by weight.

21. (New) The bone graft substitute composition of any one of claims 2, 3, and 12-20, further comprising a bone allograft.

22. (New) The bone graft substitute composition of claim 8, wherein the mixing solution is selected from a group consisting of sterile water, an inorganic salt, and a cationic surface active agent.

23. (New) The bone graft substitute composition of claim 22, wherein the cationic surface agent is selected from a group consisting of sodium chloride, phosphate buffered saline, potassium chloride, sodium sulfate, ammonium sulfate, ammonium acetate, and sodium acetate.

24. (New) The bone graft substitute composition of claim 8, wherein the mixing solution comprises sterile water.

25. (New) The bone graft substitute composition of claim 8 wherein the cellulose derivative is selected from a group consisting of sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethylcellulose and cellulose acetate butyrate.

26. (New) The bone graft substitute composition of claim 8, wherein the cellulose derivative comprises carboxymethylcellulose.

27. (New) The bone graft substitute composition of claim 8, wherein the calcium sulfate comprises calcium sulfate hemihydrate.

28. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is a growth factor.

29. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is a bone autograft.

30. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is an analgesic.

31. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is bone marrow.

32. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is a bone allograft.

33. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is parenchymal cells.

34. (New) The bone graft substitute composition of claim 8, wherein the bioactive agent is mesenchymal cells.

35. (New) A method of making a bone graft substitute composition, the method comprising:

providing a first composition comprising calcium sulfate, a cellulose derivative and demineralized bone matrix; and

contacting the first composition with a mixing solution to form the bone graft substitute composition.

36. (New) The method of claim 35, wherein the first composition further comprises a bone allograft.

37. (New) The method of claim 35, further comprising forming the bone graft substitute composition into a putty.

38. (New) The method of claim 35, wherein the calcium sulfate comprises calcium sulfate hemihydrate, the cellulose derivative comprises carboxymethylcellulose, and the mixing solution comprises sterile water.